

Attorney Docket No.: 4341.224-US  
Application No.: 10/620,651  
Filed: July 16, 2003  
Applicants: Jan Markussen et al.  
Via Facsimile : 571-273-8300

**Amendments To The Claims**

The listing of claims will replace all prior versions, and listings, of the claims in the application.

**Listing Of The Claims**

Claim 1 (Presently Amended) A pharmaceutical composition for the treatment of diabetes in a patient in need of such treatment, comprising a sodium phosphate buffer and a therapeutically effective amount of ~~a derivative of a parent insulin~~ an insulin derivative having the following sequence:

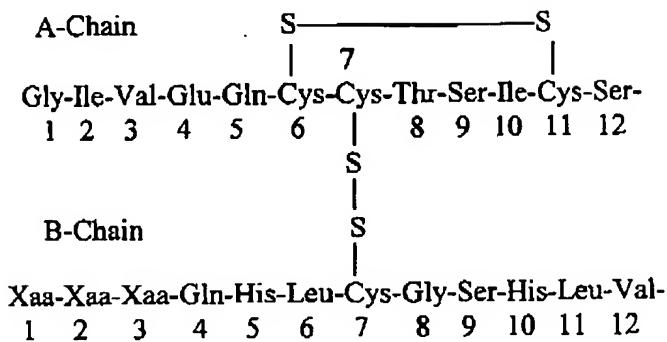
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A-Chain (contd.)

Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Xaa (SEQ ID NO:1)  
 13 14 15 16 17 18 19 | 21  
                             S

B-Chain (contd.)

Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-  
 13 14 15 16 17 18 19 20 21 22 23 24

B-Chain (contd.)

Phe-Xaa-Xaa-Xaa-Xaa-Xaa (SEQ ID NO:2)  
 25 26 27 28 29 30

wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2, B3, B26, B27, B28, B29 and B30 are, independent of each other, any codable amino acid except Cys or deleted; and a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or a

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lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged, provided that:

- (a) when B1-B2-B3 is Phe-Val-Asn and A21 is Asn and B26-B27-B28-B29-B30 is Tyr-Thr-Pro-Lys-Thr or Tyr-Thr-Pro-Lys-Ala, then the lipophilic group W or Z always contains a group which can be negatively charged; and
- (b) when B29 and B30 are deleted and the lipophilic group Z is present and B1, B2 and B3 are not deleted then B1-B2 is different from Phe-Val or B26-B27-B28 is different from Tyr-Thr-Pro or both B1-B2 and B26-B27-B28 are different from said sequences; and
- (c) when B29 and B30 are deleted and the lipophilic group Z is present and one of B1, B2 or B3 is deleted then the N-terminal amino acid of the B-chain is different from Val or the sequence B26-B27-B28 is different from Tyr-Thr-Pro or both the N-terminal amino acid of the B-chain and the sequence B26-B27-B28 are different from Val and Tyr-Thr-Pro respectively.

Claims 2-10 (Cancelled)

Claim 11 (Original) A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 1.

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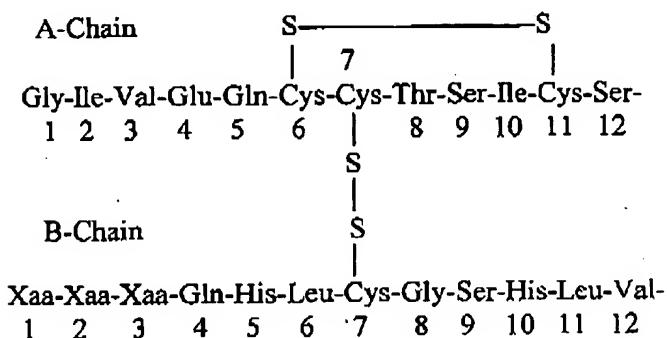
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Claim 12 (Presently Amended) A pharmaceutical composition for the treatment of diabetes in a patient in need of such treatment, comprising a therapeutically effective amount of a hexameric insulin complex which contains a derivative of a parent insulin that comprises at least one insulin derivative having the following sequence:



A-Chain (contd.)

20  
 Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Xaa (SEQ ID NO:1)  
 13    14    15    16    17    18    19    |    21  
 |  
 S

B-Chain (contd.)

Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-  
 13    14    15    16    17    18    19    20    21    22    23    24

B-Chain (contd.)

Phe-Xaa-Xaa-Xaa-Xaa-Xaa (SEQ ID NO:2)  
 25    26    27    28    29    30

wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

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Xaa at positions B1, B2, B3, B26, B27, B28, B29 and B30 are, independent of each other, any codable amino acid except Cys or deleted; and a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged, provided that

- (a) when B1-B2-B3 is Phe-Val-Asn and A21 is Asn and B26-B27-B28-B29-B30 is Tyr-Thr-Pro-Lys-Thr or Tyr-Thr-Pro-Lys-Ala, then the lipophilic group W or Z always contains a group which can be negatively charged; and
- (b) when B29 and B30 are deleted and the lipophilic group Z is present and B1, B2 and B3 are not deleted then B1-B2 is different from Phe-Val or B26-B27-B28 is different from Tyr-Thr-Pro or both B1-B2 and B26-B27-B28 are different from said sequences; and
- (c) when B29 and B30 are deleted and the lipophilic group Z is present and one of B1, B2 or B3 is deleted then the N-terminal amino acid of the B-chain is different from Val or the sequence B26-B27-B28 is different from Tyr-Thr-Pro or both the N-terminal amino acid of the B-chain and the sequence B26-B27-B28 are different from Val and Tyr-Thr-Pro respectively.

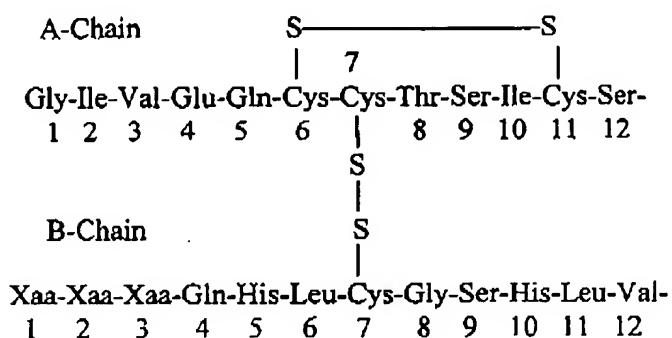
Claims 13-25 (Cancelled)

Claim 26 (Original) A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 12.

Claims 27-46 (Canceled)

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**Claim 47 (Presently Amended) A derivative of a parent insulin An insulin derivative having the following sequence:**



### A-Chain (contd.)

20  
Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Xaa (SEQ ID NO:1)  
13 14 15 16 17 18 19 | 21

### B-Chain (contd.)

Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-  
13 14 15 16 17 18 19 20 21 22 23 24

### B-Chain (contd.)

Phe-Xaa-Xaa-Xaa-Xaa-Xaa (SEQ ID NO:2)  
25 26 27 28 29 30

wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

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Xaa at positions B1, B2 and B3 are independently any codable amino acid except Cys or deleted;

Xaa at positions B26, B27, B28 and B29 are independently any codable amino acid except Cys;

Xaa at position B30 is a dipeptide which does not contain Cys or Arg, a tripeptide which does not contain Cys or Arg, or a tetrapeptide which does not contain Cys or Arg; and (a) a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or (b) a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged.

Claims 48-65 (Cancelled)

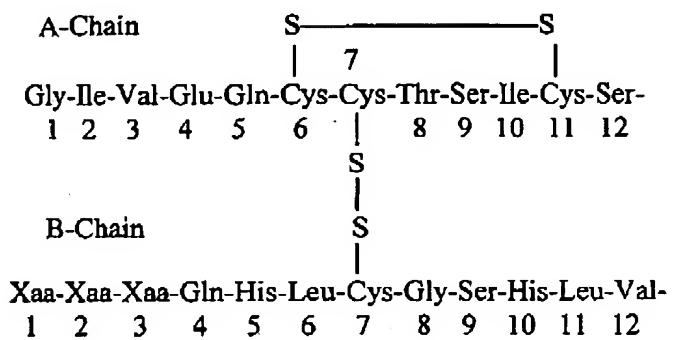
Claim 66 (Original) A pharmaceutical composition comprising a therapeutically effective amount of the derivative of claim 47 together with a pharmaceutically acceptable carrier.

Claim 67 (Cancelled)

Claim 68 (Original) A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a pharmaceutical composition of claim 66.

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**Claim 69 (Presently Amended) A derivative of a parent insulin An insulin derivative having the following sequence:**



### A-Chain (contd.)

20  
Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Xaa (SEQ ID NO:1)  
13 14 15 16 17 18 19 | 21

### B-Chain (contd.)

Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-  
 13 14 15 16 17 18 19 20 21 22 23 24

## B-Chain (contd.)

Phe-Xaa-Xaa-Xaa-Xaa-Xaa (SEQ ID NO:2)  
25 26 27 28 29 30

wherein at least one amino acid or sequence of amino acids selected from the group comprising B1, B30, B(29-30), B(28-30), B(27-30) and B(26-30) is deleted and

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

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Xaa at positions B1, B2, B3, B26, B27, B28 and B29 are independently any codable amino acid except Cys or deleted;

Xaa at position B30 is any codable amino acid except Cys, a dipeptide which does not contain Cys or Arg, a tripeptide which does not contain Cys or Arg, a tetrapeptide which does not contain Cys or Arg, or deleted; and (a) a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or (b) a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged, provided that:

(a) when B29 and B30 are deleted and a group Z as defined above is present at the C-terminal amino acid of the B-chain and neither B1, B2 nor B3 is deleted then B1-B2 is different from Phe-Val or B26-B27-B28 is different from Tyr-Thr-Pro or both B1-B2 and B26-B27-B28 are different from said sequences; and

(b) when B29 and B30 are deleted and a group Z as defined above is present at the C-terminal amino acid of the B-chain and one of B1, B2 or B3 is deleted then the N-terminal amino acid of the B-chain is different from Val or the sequence B26-B27-B28 is different from Tyr-Thr-Pro or both the N-terminal amino acid of the B-chain and the sequence B26-B27-B28 are different from Val and Tyr-Thr-Pro respectively.

Claims 70-91 (Cancelled)

Claim 92 (Original) A pharmaceutical composition, comprising a therapeutically effective amount of the derivative of claim 69 together with a pharmaceutically acceptable carrier.

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Claim 93 (Cancelled)

Claim 94 (Original) A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a pharmaceutical composition of claim 92.

Claims 95-116 (Canceled)

Claim 117 (Presently Amended) ~~A derivative of a parent insulin~~ An insulin derivative having the following sequence:

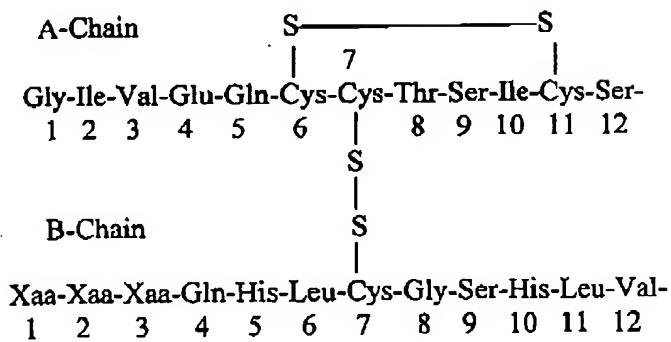
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### A-Chain (contd.)

20  
Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Xaa (SEQ ID NO:1)  
13 14 15 16 17 18 19 | 21

### B-Chain (contd.)

Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-  
 13 14 15 16 17 18 19 20 21 22 23 24

### B-Chain (contd.)

Phe-Xaa-Xaa-Xaa-Xaa-Xaa (SEQ ID NO:2)  
25 26 27 28 29 30

wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2 and B3 are independently any codable amino acid except Cys or

deleted;

Xaa at positions B26, B27, B28 and B29 are independently any codable amino acid except Cys;

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Xaa at position B30 is Lys; and (a) a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or (b) a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged.

**Claims 118-133 (Cancelled)**

**Claim 134 (Original)** A pharmaceutical composition, comprising a therapeutically effective amount of the derivative of claim 117 together with a pharmaceutically acceptable carrier.

**Claim 135 (Cancelled)**

**Claim 136 (Original)** A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient the pharmaceutical composition of claim 134.